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CHOOSING A PERCENTILE OF ACUTE DIETARY EXPOSURE AS A THRESHOLD OF REGULATORY CONCERN

(DRAFT 4/1/99)

EXECUTIVE SUMMARY

EPA is responsible for regulating the nature and amount of pesticide residues in food under the Federal Food, Drug and Cosmetic Act (FFDCA). FFDCA sec. 408 authorizes EPA to set a tolerance or an exemption from the requirement of a tolerance if the Agency determines that the residues would be "safe." The Agency performs various types of risk assessments to evaluate the safety of pesticides in food, including analyses to determine the nature and the amounts of pesticides that people might be exposed to over a single day. This paper discusses how EPA applies the statutory safety standard to acute dietary risk assessments.

The Environmental Protection Agency's Office of Pesticide Programs (OPP) has previously announced that, on an interim basis, it intends to regulate pesticides at the 99.9th percentile of the distribution of estimated acute dietary exposures when probabilistic assessment techniques are used to model the distribution. EPA will compare this percentile of estimated exposure to the Population Adjusted Dose (PAD), a value that reflects an amount of a pesticide to which a person may safely be exposed in one day. This draft science policy paper describes OPP's interim policy, concerns that have been raised about it, associated public health issues, and OPP's plans for further evaluation and implementation. This policy has broad applicability to many pesticides and potentially significant impact on the assessment of these pesticides. Moreover, a number of concerns and issues have been raised about the policy. Therefore, the Agency is seeking public comment so that OPP policy is transparent and that the views of all interested parties are considered.

OPP's interim position with respect to assessing and regulating the food uses of pesticides, when using a probabilistic method of estimating acute dietary exposure, is as follows:

> If the 99.9th percentile of acute dietary exposure (together with exposure from other non-dietary, non-occupational sources), as estimated by probabilistic (e.g., Monte Carlo) analysis, is ***equal to or less than*** the Population Adjusted Dose (PAD) for the pesticide, OPP will determine that the safety standard of FFDCA sec. 408(B)(2)(A) is met with respect to acute dietary risk. However, if the analysis indicates that exposure at the 99.9th percentile ***exceeds*** the PAD, OPP

will conduct a sensitivity analysis to determine to what extent the estimated exposures at the high-end percentiles may be affected by unusually high food consumption or residue values. To the extent that one or a few values from the input data sets seem to "drive" the exposure estimates at the high end of exposure, OPP will consider whether these values are representative and should be used as the primary basis for regulatory decision making. The Office will also examine the consequence of removing such high-end food consumption or residue values when estimating the 99.9th percentile of exposure.

Section I of this paper provides an overview of OPP's present practice and interim policy for acute dietary risk assessment. It describes the statutory, regulatory and policy framework for this interim policy, as well as prior reviews and comments. In addition, this section provides background information on dietary risk assessment in general and explains how the previous system (DRES--Dietary Risk Evaluation System) and the current system (DEEM--Dietary Exposure Estimating Model) work, as well as what input data sources are used and how.

Section II addresses some of the specific issues and concerns raised about regulating at the 99.9th percentile. One issue is whether the nature of the databases available (i.e., robustness, adequacy, etc.) should preclude the use of the 99.9th percentile for regulatory purposes since some consider the uncertainties associated with this threshold of concern to be too great. Examples of data used are USDA's food consumption survey data, registrant crop field trials, USDA Pesticide Data Program (PDP) data, FDA monitoring data, market basket surveys, etc. Other issues include the treatment of data "outliers," representativeness and adequacy of the databases, and the impact of Agency default values on exposure estimates. Concerns, therefore, exist about whether the estimates of the 99.9th percentile of exposure are sufficiently representative of actual exposure to be meaningful. This paper summarizes these concerns and invites comment on them.

Section III addresses the issue of protectiveness of the 99.9th percentile with respect to the general public health. One view is that regulating at the 99.9th percentile is insufficiently conservative because very large numbers of people could be exposed every day to pesticide intakes which are estimated to exceed the Agency's "level of concern." This section also explores the contrary view – that the interim policy is over-protective because of the conservative assumptions used in the estimation methods and the retention of potentially unrepresentative values in the data base. The section discusses as well as the view that, whether it over- or under-estimates actual exposure, the 99.9th percentile is simply too uncertain to be used in risk management decisions.

Section III also explains that OPP considers a number of factors in considering which percentile to use: the size of the exposed population and the proportion that might receive daily doses above the benchmark of safety, the aRfD; the level of confidence OPP has in its exposure estimates; and the extent to which such estimates may overstate potential exposure because they incorporate conservative assumptions or rely on atypical and unrealistic data. Further, to the

extent understood, OPP considers by how much individual exposures would be estimated to exceed the aRfD. Finally, the OPP takes into account the degree of public health protection incorporated into the determination of the aRfD.

Section IV addresses the areas in which OPP and USDA propose to collaborate in performing further exploratory analysis with the DEEM software and the 99.9th percentile issue.

Section V lists questions and issues on which the Agency would most like commenters to focus and respond.

Section VI provides a list of the documents referenced in this paper.

The Appendix, entitled "Primer on Interpretation of Exposure Distribution Curves," is a "plain English" guide to Monte Carlo analysis and how to interpret results from it.

I. OPP's Present Practice and Interim Policy for Acute Dietary Risk Assessment

A. Introduction

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), the Environmental Protection Agency may authorize a tolerance or exemption from the requirement of a tolerance, to allow a pesticide residue in food, only if the Agency determines that such residues would be "safe" (FFDCA sec. 408(b)(2)(A)(I)). The term "safe" is defined as a "reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including dietary exposures and all other exposures for which there is reliable information" (FFDCA sec. 408(b)(2)(A)(ii)).

To determine whether food is safe to eat, OPP must assess the potential risks from pesticide residues in food. The size of the potential risks depends on the toxicity of the pesticide (how much harm, if any, is caused by specific amounts of the pesticide) and the magnitude of the exposure to the pesticide. Exposure to a pesticide in the food supply depends, in turn, on two factors: the amount of the pesticide present in food and how much food a person eats. It is impossible to know precisely how much food every individual in the country consumes, either over a lifetime or even on a single day. Similarly, it is impossible to know how much residue each specific item of food contains. Thus, the Agency must use available and reliable, representative data to develop estimates of such exposure.

In evaluating the potential risks from pesticides in the diet, OPP assesses both chronic (long term) exposure and acute (short term) exposure. For chronic exposure, OPP estimates the average amount of pesticide residue a person might consume over extended periods, ranging from several years to a lifetime. For acute exposure, OPP is instead interested in the amount that might be ingested on a single day. To evaluate acute dietary exposure, OPP now uses a probabilistic exposure modeling technique, an example of which is "Monte Carlo analysis." For

the purpose of discussion, this paper will use the term “Monte Carlo” keeping in mind that other probabilistic techniques may be used as well. This probabilistic assessment technique estimates the different levels of exposure people experience as the result of differences in the types and amount of foods they eat, as well as variations in the level of pesticide residue that may be present, among other factors.

Over the last several years, OPP has been working to expand its capability of evaluating acute dietary exposure and risk using probabilistic techniques of assessment. In early 1998, OPP established an interim policy and a series of guiding principles for the use of probabilistic risk assessment techniques. In part, this policy was based on Agency policy regarding the use of probabilistic techniques in risk assessment. Specifically, in a 1997 memorandum from Deputy Administrator Fred Hansen, EPA stated that probabilistic analysis techniques, "given adequate supporting data and credible assumptions, can be viable statistical tools for analyzing variability and uncertainty in risk assessments" (U.S. EPA, 1997). The Agency also enumerated a set of conditions to be considered in judging the acceptability of a probabilistic analysis for review and evaluation; these conditions relate to transparency, reproducibility and the use of sound methods (U.S.EPA, 1997a). This Agency policy document noted that Monte Carlo analysis is the only probabilistic technique that has been accepted so far, but EPA would be open to considering other probabilistic techniques.

Among other things, the interim policy document indicated that, when probabilistic exposure assessments were available for acute dietary risk, the Agency would refer to the 99.9th percentile of estimated exposure in making its risk management decisions. In general,OPP would compare this level of exposure to a safety benchmark, e.g., the acute Reference Dose (aRfD), in determining whether a particular regulatory action would be consistent with the statutory safety standard.

B. Previous Review of OPP’s Interim Policy

In March 1998, OPP brought its interim policy to the FIFRA Scientific Advisory Panel (SAP). The SAP generally agreed with the probabilistic approach proposed by the Office. They considered, among other things, the issue of where it might be appropriate to regulate and expressed divergent views on whether using the 99.9th percentile as a regulatory criterion is an (adequately) conservative approach. They noted that, in their view, if the 99.9th percentile is utilized, a percentage of the population could still be exposed daily to estimated levels that exceed the regulatory threshold of concern. They further noted that, even though the percentage was small (0.1%), the number of people represented by that percentage was very large because the exposed group is potentially the entire population of the country. The following additional remarks were made by the Panel:

- To judge whether any given percentile criterion is conservative for acute effects or not, it would be necessary to consider the margin of safety which is already incorporated into the toxicological portion of the risk evaluation.

- To identify the level of risk, variability not only in exposure levels but also in human thresholds for the toxic effects under consideration would be needed. That is, a probabilistic "toxicity" component of a risk assessment should be incorporated into the analysis as well.

- The panel pointed out that by recognizing and separately modeling subpopulations, it may be possible to choose a lower, less statistically tenuous percentile at which to make regulatory decisions for one or more of these subpopulations. This lower percentile may also be warranted, they indicate, if the risk assessment contains a number of "conservative" assumptions that might result in overestimates of risk even at the 99.9th percentile.

The Agency's approach to acute dietary risk assessment has been discussed extensively by the Tolerance Reassessment Advisory Committee. In addition, in January 1998 the FQPA Implementation Working Group (IWG), an informal coalition of agricultural commodity groups and food processing and agricultural chemical trade associations, submitted comments to OPP addressing OPP's approach to managing acute dietary risks. In particular, the IWG asserted that the residue and food consumption data sets used as input for probabilistic exposure techniques contained data points which were "outliers" and which made the resulting estimates of exposure distribution appear unrealistically high. IWG also argued that other conservative assumptions (assumptions that would likely overstate potential exposure) used in developing the exposure estimates made the use of the 99.9th percentile an inappropriate point of reference for regulatory decision making.

Following the SAP review and after considering public comment, OPP revised portions of its interim policy document. This revised document incorporated many of the changes recommended by the SAP in its March 1998 meeting discussed above. On November 5, 1998, EPA announced in the *Federal Register* (63 FR 59780) the availability of the revised document as a draft science policy paper entitled "Guidance for Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs." As its title indicates, the science policy paper contained guidance on the submission of exposure assessments; it also stated that OPP would present separately an explanation of its policy decision to refer to the 99.9th percentile of estimated acute dietary exposure in making its risk management decisions. This document addresses this latter issue.

The Agency and the U. S. Department of Agriculture (USDA) have also discussed the OPP policy with respect to determining a level of concern for regulatory decisions about the risks of acute exposure to pesticides in the diet. USDA has commented that the use of data bases which contain too few data points to project high end percentiles of consumption of a particular food or levels of residues in a specific commodity with statistical confidence raises questions about the estimates of high end exposure developed using probabilistic assessment techniques. At their worst, USDA has indicated that such outputs could be meaningless in terms of numerical

representations of population exposure. EPA has considered USDA's comments and revised this paper to explain and address their concerns.

C. OPP's Current Approach to Dietary Risk Assessment

1. Chronic vs. Acute Exposure and Risk Assessment

OPP typically performs a dietary exposure assessment for two different exposure time frames -- short term or "acute" exposures and long-term or "chronic" exposures; each assessment is calculated differently. In chronic exposure assessment, the risk assessor is attempting to estimate a person's average dietary exposure over the long-term (e.g., several years to a lifetime). Consequently, the use of both average (or mean) residue value for each food commodity and average (or mean) consumption of food commodities is generally regarded as appropriate (estimates of exposure through drinking water are subsequently combined with these estimates of exposure through food to calculate combined exposure through food and water). In acute dietary exposure assessment, however, the risk assessor is trying to estimate the range of exposures that individuals could encounter on a single day and determine the exposure to which "high-end" persons could be subjected (where "high-end" is defined as a plausible estimate of exposure for those individuals at the upper end of the exposure distribution). The Office is using Monte Carlo techniques (and its current 99.9th percentile approach) for these acute exposure assessments only. OPP is not using Monte Carlo techniques at this time for chronic exposures due to the limitations of the existing food consumption data. EPA and USDA, however, are exploring statistical techniques that may allow such analyses in the future. The Monte Carlo Guidance document provides additional information regarding the tiering process used in acute assessments, for both probabilistic and non-probabilistic assessments.

Units of Measure

mg/kg bw/day. Milligrams of pesticide per kilogram of body weight per day.

μg. Microgram.

g. Grams

Measures of Toxicity

aRfD. An amount of toxicant (in mg/kg bw/day) to which a person can be safely exposed for one day

NOAEL. Largest amount of toxicant (again in mg/kg bw/day) in a controlled toxicological study which produces no adverse effect in a test animal

Uncertainty Factor. A series of safety factors by which the NOAEL is reduced to obtain the aRfD. Usually, these consist of an interspecies factor (10x) and an intra-species factor (10x).

2. The Risk Equation

Dietary risk can be expressed as a function of toxicity and exposure.

RISK = f (toxicity, exposure)

That is, to determine risk – which can be either acute (one-day) or chronic (long-term) – one "multiplies" the toxicity value for the pesticide by the amount of pesticide to which an individual is exposed.

The ***toxicity*** part of the risk equation is typically expressed as an acute reference dose (aRfD, in units of mg/kg body weight per day). An aRfD is an amount of toxicant (in mg/kg bw/day) to which a person can be safely exposed for one day. In general, an aRfD is set at a level

at least 100 times smaller than the no-observed-adverse-affect level (NOAEL, in units of mg/kg bw/day), if the NOAEL used is from a controlled toxicological study in laboratory animals. The NOAEL is defined as the largest amount of toxicant (in units of mg/kg bw/day) which produces no observed adverse effects. The factor of 100 is a generally applied adjustment, (sometimes called a "safety factor" or, more frequently, an "uncertainty factor") to account for the potential that humans could be more sensitive to the toxic effects of a compound than laboratory test animals (10 X) and that some humans could be more sensitive than others (10 X).

The dietary (food) ***exposure*** part of the equation is derived from two distinct pieces of information: the amount of pesticide residue that is present in and on food (i.e., the residue level) and the types and amounts of food in a person's diet (i.e., food consumption). The residue information comes mainly from the numerous crop field trials submitted by pesticide manufacturers and USDA or from monitoring data collected by the USDA and FDA (see Section I.C.3.(b)). Consumption information comes primarily from USDA surveys of what people eat (see Section I.C.3.(a)).

The basic equations for acute dietary (food) risk assessment are:

$$Exposure\ (mg/kg\ bw/day) = Consumption\ (kg\ food/kg\ bw/day)\ x\ Residue\ (mg\ pesticide/kg\ food)$$

$$aRfD\ (mg/kg\ bw/day) = \frac{NOAEL\ (mg/kg\ bw/day)}{interspp.\ factor\ (10x)\ x\ intraspp.\ (10x)\ factor}$$

$$Population\ Adjusted\ Dose\ (PAD)\ (mg/kg\ bw/day) = \frac{aRfD\ (mg/kg\ bw/day)}{FQPA\ Factor}$$

$$\%\ PAD = \frac{Exposure\ (mg/kg\ bw/day)}{PAD\ (mg/kg\ bw/day)}\ x\ 100$$

NOTE: Once the aRfD is derived, the population for which the assessment is being done is identified. If this population includes the fetus, infants and/or children, a determination concerning retention, reduction, raising or removal of the FQPA 10X Safety Factor must be made. The resulting allowable exposure is termed the Population Adjusted Dose (PAD). If it is deemed appropriate to remove the FQPA 10X Safety Factor, then the PAD will be the same as the aRfD. If it is deemed appropriate to retain the FQPA 10X Safety Factor, then the PAD would be 10% of the aRfD. If it is deemed appropriate to reduce the FQPA 10X Safety Factor, e.g. by 3-fold, then the resulting PAD would be reduced by the same fold factor, in this case to 33% of the aRfD. If the population under evaluation does not include the fetus, infants and/or children, or women of

child-bearing age, then the PAD would be the same as the aRfD. The PAD represents the level of exposure during one day at which no harm would be expected to occur.

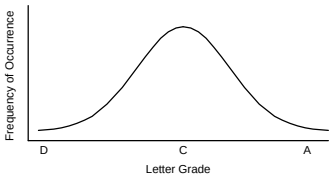
The value of the" %PAD" reflects the relative size of the PAD and the estimated exposure. If the estimated exposure is ***less*** than the PAD, the value will be below 100%. Conversely, if the exposure is estimated to ***exceed*** the PAD, the value will be greater than 100%. Traditionally, if the "%PAD" is less than 100%, the estimated exposure is considered "safe" in those cases where it is deemed appropriate to remove the FQPA 10x factor.

3. Data Bases Used in Probabilistic Dietary Exposure Estimates

Currently, OPP is developing acute, probabilistic dietary exposure assessments using Monte Carlo techniques that require data on (1) the *distribution* of daily consumption of specific commodities (wheat, corn, apples, etc.) by specific individuals (in g commodity/kg bw/day), and (2) the *distribution* of concentrations of a specific pesticide in those food commodities (in μg pesticide/g commodity). The latter information is generally obtained from crop field trials, USDA PDP or FDA monitoring data, market basket surveys conducted by the registrants, and other sources while the former is collected by USDA in its Continuing Survey of Food Intake by Individuals (CSFII). These two input data sources, the USDA CSFII and the residue data sources, are discussed below.

What Does the Term *Distribution* Mean?

Think back to the classic bell curve we learned about at some point in our school days. When grades were being determined, some of us had scores that were either on the low -end or high-end of the range while most of us had scores in the middle. If the frequency of occurrence were plotted, the resulting distribution of grades would resemble the bell curve: Essentially what the bell curve tells



us is that most things are near the middle – there are far fewer occurrences at the extremes.

(a) *Food Consumption: USDA Continuing Survey of Food Intake by Individuals*

The food survey data used in the Office's probabilistic exposure and risk assessments are collected by the U.S. Department of Agriculture and are currently from the 1989-91 Continuing Survey of Food Intake by Individuals (CSFII)[1]. The 1989-91 CSFII, conducted as three separate 1-year surveys in 1989, 1990 and 1991, was designed to measure what Americans eat and drink. The USDA has been conducting such food surveys since the 1930's by means of personal interviews in which interviewers ask individuals to recall everything they ate and drank over the previous 24 hours. The uses of Food Survey Research Group survey data are varied and include the assessment of dietary intakes, dietary trends and food consumption economics; the development of policies for food assistance, food labeling and food safety programs; and the implementation of dietary guidance and nutrition education programs. Information from the surveys also is widely used across the U.S. to develop nutrition and education programs, to assess dietary changes associated with participation in food programs, to

[1] Data from the recently completed 1994-96 CSFII have now been released by USDA and are expected to be incorporated into the OPP's risk assessments beginning in Spring, 1999.

develop food fortification and enrichment policies, to monitor the safety of the food supply, and to assess demand for agricultural products and marketing facilities. In accordance with federal data reporting guidelines (USDA needs to provide a cite), USDA identifies and cautions users of its databases about the lack of adequate numbers of data points for certain statistical projections. For example, some of the commodities for which EPA sets tolerances are eaten so infrequently that USDA cautions against using the survey data to estimate high-end percentiles of consumption of such commodities, e.g. the 95^{th} percentile or greater.

CSFII (1989-91) data are derived from information provided by 15,128 individuals who participated in the survey. One-day food and nutrient intake data for individual of all ages were collected between April 1989 and March 1992. Individuals who took part in the survey were asked to provide three consecutive days of dietary data. The first day's data were collected in a personal in-home interview using a 1-day dietary recall. The second and third days' data were collected using a self-administered 2-day dietary record. Intake amounts were reported and energy and nutrient intakes were calculated using the USDA Nutrient Data Base for Individual Intake Surveys. Subject to the cautions about statistical treatment of data, the data collected for such large numbers of survey participants, who have been scientifically selected so that results could be projected from the sample to the U.S. population, constitute a reliable and representative national sample.

(b) *Residue Data Sources: Field Trials, Monitoring and Market Basket Surveys*

In addition to the food consumption data provided by USDA's CSFII, information on the distribution of residue levels in foods is necessary in order to calculate dietary exposure and risk in a probabilistic manner. Data on the distribution of residues on foods for use in OPP's probabilistic exposure and risk assessments can be obtained from a variety of sources including: (1) crop field trials, (2) FDA enforcement monitoring, (3) USDA PDP monitoring, (4) specialized market basket surveys (usually conducted by the pesticide registrant), and (5) studies on the effects of commercial processing, peeling, washing, cooking or other activities that may affect residue levels. Crop field trials are experimental trials, usually performed by a pesticide company or USDA, in which the maximum usage scenario (with respect to application rate, number of applications, pre-harvest interval, etc.) is simulated. These OPP-required experimental trials are conducted according to Agency guidelines, primarily to determine maximum residues that may be present in fruit, vegetable, grain and other food and feed crops at the earliest point where these food commodities could enter commerce. These data are used to establish legally-enforceable pesticide tolerance limits.

In contrast to the pesticide residue data collected during the experimental field trials, FDA and USDA pesticide monitoring data (as well as registrant-sponsored, market basket survey data) represent residue data in crops collected from commercial trading channels (wholesalers, warehouses, distribution centers, retailers, etc.). These data better represent pesticide residues to which consumers are actually exposed because they measure residues in food in commercial channels rather than residue levels resulting from experimental field trials conducted under

maximum application scenarios.

The Office prefers to use data from FDA or USDA PDP monitoring data or market basket surveys, when available, in calculating pesticide exposure estimates. However, these data are not always available or appropriate for use; when this is the case, OPP uses pesticide residue data collected from the experimental field trials. As the field trial data represent residues resulting from a maximum application scenario to which only very few crops are actually subjected, OPP may refine these data to take into account other factors such as residue degradation as a result of transport or storage, or variabilities in farming practices such as use of longer than label pre-harvest intervals and lower than label application rates. In addition, OPP's exposure estimates can be modified or adjusted, as appropriate, to take into account decreasing or increasing concentrations in processed commodities as a result of commercial processing practices or decreased residues as a result of cooking or in-home preparation such as washing, peeling, coring etc. Finally, information on the percent of the crop which is treated, if available, is also used to adjust the probability of encountering a treated commodity.

4. DRES and DEEM

Until recently, OPP used a software program called the Dietary Risk Evaluation System (DRES) to conduct its acute dietary (food) risk assessments. Assessments conducted with DRES assumed that 100% of a given crop with registered uses of a pesticide was treated with that pesticide and that all such treated crop items contained pesticide residues at the maximum legal (tolerance) level. The resulting DRES acute risk estimates were considered "high-end" or "bounding" estimates.[2] However, it was not possible to know where the pesticide exposure estimates from the DRES software fit in the overall *distribution* of exposures due to the limits of the tools being used. Thus, risk management decisions were being made not only without a full picture of the distribution of risk among the population, but also without full knowledge of where in the distribution of risk the DRES risk estimate lay.

OPP is now using the Dietary Exposure Evaluation Model (DEEM) computer software program for its dietary (food) exposure and risk assessments. Like the DRES model, DEEM calculates acute and chronic dietary risk using the inputs of: pesticide residues in and on food, food consumption and toxicity. Also, like DRES, DEEM is able to calculate an estimate of the risk to the general U.S. population in addition to 26 population subgroups, including five subgroups for infants and children:

[2] A "high-end" estimate is one that is, conceptually, above the 90th percentile of the actual exposure distribution but not greater than the exposure to the person in the population who has the highest exposure. It is a plausible estimate of the individual exposure for those persons at the upper end of the exposure distribution. A "bounding estimate," on the other hand, purposely overestimates the exposure or dose in an actual population for the purpose of developing a statement that the risk is "not greater than..." (U.S. EPA, 1992. Guidance on Risk Characterization for Risk Managers and Risk Assessors).

• U.S. population	• children 7-12	• Females 13+, pregnant/not nursing
• U.S. population -spring	• Hispanics	• Females 13+ nursing
• U.S. population--summer	• Non-Hispanic Whites	• Males, 13-19
• U.S. population--autumn	• Non-Hispanic Blacks	• Males 20+
• U.S. population--winter	• Non-Hispanic (other than Black or White)	• Seniors 55+
• all infants	• Females 13-19, not pregnant or nursing	• Northeast
• nursing infants (<1 yr)	• Females 20+, not pregnant or nursing	• Midwest
• non-nursing infants (<1 year)	• Females 13-50	• South
• children 1-6	• Pacific	• West

Unlike DRES, DEEM can generate ***probabilistic*** assessments of acute dietary exposure. DEEM uses a mathematical technique called Monte Carlo analysis to generate estimates of the *distribution* of pesticide dietary exposures. That is, it uses all the individual food consumption and pesticide residue level data points included in a data set to determine the combined (or joint) distribution of exposures (and associated risk). For more information on the interpretation of exposure distribution curves generated by the DEEM software, see Appendix I - "Primer on Interpretation of Exposure Distribution Curves." At this time, OPP uses DEEM to develop probabilistic exposure estimates only for *acute* assessments.

The Monte Carlo technique provides a relatively new tool for more accurately estimating the complete distribution of exposures, and provides probabilistic and statistical assessment of dietary risk using more refined information than was used previously. This analysis uses the actual distribution of pesticide residue levels from either the experimental field trials performed by the registrant or monitoring or market basket surveys whereas in DRES only a high-end residue value was used. Also, it can incorporate information on the percentage of the crop which is treated. That is, it includes the actual distribution of possible consumption and residue values and weighs these possible values by their *probability* of occurrence. Using Monte Carlo, OPP does not assume (as was previously required with DRES) that all registered crops are treated with the pesticide of interest or that all residues are present in crops at maximum legal (tolerance) levels. Rather than the crude "high-end," single point estimates provided by DRES, Monte Carlo provides more accurate information on the range and probability of possible exposure and their associated risk values.

Monte Carlo techniques are, in and of themselves, neither more conservative nor less conservative than the DRES system they supplement: the "conservatism" is determined by the risk

manager when he or she determines the appropriate percentile of the model's output distribution (e.g., 99.9th percentile) to be used for regulation. Monte Carlo and probabilistic techniques are simply tools that allow the risk assessor and manager to see a more accurate distribution of risks among the general population and subpopulations.

5. DRES 95th Percentile vs. Monte Carlo 99.9th Percentile

The Agency has in the past regulated at the 95th percentile of an acute DRES analysis. Concerns have been raised about what is seen by some as a significant "raising of the bar" by now choosing to refer to the 99.9th percentile from a Monte Carlo analysis. While it may appear at first that the Agency is taking a more stringent approach, this is actually not so. Exposure at the 99.9th percentile (as calculated by Monte Carlo) is significantly lower than exposure calculated by DRES at the 95th percentile for most cases reviewed by OPP to date. There are several reasons for this. An acute DRES analysis assumes that:

- Residues are present at tolerance levels in all crops that have registered uses; and

- All the crop is treated at the maximum (label) application rate and is harvested at the minimum (label) pre-harvest interval (i.e., the time period between last application and harvest).

In general, Monte Carlo techniques will provide lower and more realistic estimates of exposure than previous DRES techniques when:

- a lower percentage of the crop is treated (e.g., 10% rather than 100%);

- a greater number of crops are registered (e.g., 10 crops instead of 2 crops); and

- The bulk of residue values from crop field trials are present at low levels and there are only a few high values.

For example, a given food item (e.g., apples) can have several dozen or more individual residue values generated from experimental field trials for a certain pesticide. In an acute DRES analysis, only the highest residue value (or tolerance level) would be used and all registered crops would be assumed to be treated and contain these high residue values. In a Monte Carlo run, the entire set of actual residue data points generated by the registrant in the crop field trials and the percent of the crop which was treated would be considered. The differences between the exposure numbers generated by these two techniques can be substantial, with the Monte Carlo generated values (at the 99.9th percentile) frequently many times lower than DRES-generated values (at the 95th percentile). A table illustrating some of these extensive differences in exposure estimates for a widely used agricultural pesticide which was recently evaluated by OPP is shown below:

Comparison of DRES 95th Percentile Exposure And %aRfD Estimates with Monte Carlo 99.9th Percentile Exposure and %aRfD Estimates for One-Widely Used Agricultural Pesticide

Population Subgroup	Exposure (mg/kg bw/day)		%aRfD[a]	
	DRES 95th Percentile Estimate	Monte Carlo 99.9th Percentile Estimate	DRES 95th Percentile Estimate	Monte Carlo 99.9th Percentile Estimate
U.S. Population	0.005	0.000542	300	32
Infants	0.008	0.000804	480	48
Children 1-6	0.008	0.000905	480	54
Females 13+	0.0036	0.000468	216	28
Males 13+	0.0038	--[b]	228	--[b]

[a]The %aRfD represents the portion of the acute risk cup which is occupied. The %aRfD is obtained by dividing the estimated exposure at any given percentile (e.g., 95th or 99.9th percentile) by the aRfD. It should be remembered that the aRfD may be modified to reflect the decision with regard to the FQPA 10x Safety Factor. Comparison of the estimated exposure to the resulting Population Adjusted Dose (PAD) is then done to determine the acceptability of that exposure.
[b] not calculated

As can be seen, estimated exposures (and corresponding %aRfD's) are significantly lower at the 99.9th percentile DEEM/Monte Carlo analysis than they are at the 95th percentile DRES analysis. This is almost invariably the case. In fact, at all comparable percentiles, the exposure estimates derived from DEEM/Monte Carlo are lower than the corresponding DRES estimates. The advantage of this probabilistic technique is that it can refine the exposure and risk estimates by more fully incorporating all available information and minimizing reliance on values chosen more for their regulatory and administrative convenience than their scientific merit.

In short, DEEM/Monte Carlo analysis tends to provide a lower (but more reliable) estimate of actual exposure in exactly those situations where DRES is least realistic. OPP will continue to regulate at the DRES 95th percentile when actual tolerance levels and 100% crop treated assumptions are used during exposure assessment, but recognizes that this approach can significantly overestimate actual exposure levels. In those cases where DRES exposure estimates are greater than the regulatory threshold of concern, OPP's interim policy is to use Monte Carlo techniques to assess exposure at the 99.9th percentile using more refined data. In practice, risk assessments done at the 99.9th percentile using more refined data almost invariably result in lower estimated exposures (and corresponding estimated risk) than assessments performed at the 95th percentile using DRES and less refined data.

II. Issues Related to the Methodology and Data Bases Used in Acute Dietary Risk Assessment

Concerns have been raised among the academic, public health, industry and grower communities with regard to the appropriateness of the 99.9th percentile as the default decision point for regulation when using probabilistic techniques for acute dietary risk assessment. Specifically, these concerns include: the presence of "outliers" in the pesticide residue and food consumption data; the representativeness of the data sets used in Agency risk assessments; the limited size of the input data bases; the reliance on "uncertain" consumption values which fall at the extreme tails of the distribution when generating exposure estimates; and the degree to which the Agency's 99.9th percentile estimate incorporates conservative default assumptions. Because of these areas of concern, issues have also been raised about the interpretation of the output developed by the Monte Carlo technique. Some contend that, if the input data are not reliable and representative, neither are the outputs of any technique using such data. Therefore, they contend that the Agency should not use the 99.9th percentile of estimated exposure as a starting point for regulatory decision making and/or should make adjustments in the data sets which are inputs to the exposure assessment. Specific concerns addressed in this section include the following:

- Inclusion of high-end values from USDA food consumption input data sets (see section II.A.);
- Agency use of upper-end residue data (see section II.B.);
- Agency consideration of the size and representativeness of the data bases for consumption estimates and residue profiles (see sections II.C. and D.); and
- Agency use of conservative default assumptions in treatment of pesticide residue data (see section II.E.).

A. Treatment of High-End Consumption Values ("Outliers") in USDA CSFII Survey

Concern has been expressed that the USDA's food consumption data have not been properly evaluated to identify potential errors in the data sets or to assess the potential impacts of outliers on the estimated 99.9th percentile of exposure. As a result, it is contended by some that errors are propagated throughout the Agency's Monte Carlo analysis resulting in distributions which inappropriately and artificially inflate estimates of risks at the upper ends of the distribution. Consequently, some believe that tests for outliers must be conducted, and "outliers" should be removed from the data set, so that the high end of estimated risk is not defined by the outliers. They state that OPP's failure to do this means that the results may not be reliable or scientifically-based.

What's An Outlier?

In a data set, an *outlier* is a number that greatly differs (or is substantially removed) from the bulk of a data set. That is, it is a value that is much larger or much smaller than most of the other numbers in the set. It does not necessarily represent an invalid data point, but may simply represent an unusual or rare, but still very real, occurrence.

The Agency shares this basic concern and does not want to use data which are not reliable measures of food consumption. By the same token, OPP does not want to ignore data which measure real, but relatively infrequent, consumption events.

Anytime a survey as extensive as USDA's CSFII is conducted, high consumers of a particular food item will be found and reported. It is also true that some portion of the food consumption reports in the initial database may be erroneous. Thus, outliers may be present in the raw survey data. Given that very high energy intakes do occur in the American population (even though they are not common), considerable judgment is required to determine whether a high-end value should be declared in error and discarded or should be retained.

To assure that the CSFII data base is free of erroneous or unreliable data points, the USDA extensively validates and cross-checks any questionable survey results prior to their insertion into the CSFII database. For example, USDA survey interviewers are trained to probe for additional information when unusual intakes of various kinds are reported, and to ask questions clarifying large reported amounts, and also if the day's intake was typical or not. If not typical, queries are made about what was atypical, such as the occurrence of a holiday, a social occasion, or the like. On preliminary review of survey data, USDA identifies high intakes in various areas (i.e., high consumption of certain foods or high energy intake) and evaluates the reported intake for feasibility, including notations made by the survey interviewer relating to the perceived validity of the reported consumption. USDA carefully reviews all of the data resulting from its CSFII survey to assure that the reported results are as close to reality as possible. USDA pays particular attention to data points that may be "outliers," and that may need to be removed to characterize food consumption accurately. All reported high intake values have been checked by USDA and resolution or adjudication of values outside specified ranges have been accomplished. Thus, the USDA CSFII data base has been properly evaluated and contains accurate and reliable consumption values that, by FQPA standards, are acceptable for use in OPP's assessment of human dietary exposure to pesticide residues.

The Office also recognizes that unusually high intakes can potentially "drive" calculated exposure and risk estimates and believes that it may be inappropriate to base risk management decisions on unusual consumption values, particularly if these consumption values dominate high-end exposure estimates. Therefore, OPP is proposing that risk characterizations include a sensitivity analysis which will take advantage of a recent upgrade to the DEEM software program which is now capable of generating a "Critical Exposure Contribution" (CEC) analysis when run in the acute Monte Carlo mode. The CEC provides insights into the sources contributing to the exposure estimated for the most highly exposed people in the exposure distribution. This listing contains a detailed exposure analysis for approximately 100 individuals having a total exposure greater than a user-specified "CEC exposure value" (at present, typically around the 99.9th percentile of exposure) in the user distribution profile. The display includes key demographic information (gender, age, body weight), the food(s) consumed, amount consumed, the residue value, the total daily exposure estimate, and the exposure estimate by food. Thus, the CEC provides the Agency with comprehensive information on foods (and food-forms) that account for

the largest portion of the person's estimated exposure. If OPP finds that the high-end exposures are principally driven by suspect high-end consumption values, the Agency's risk mitigation decisions can appropriately consider and weigh these factors.

B. Treatment of High-End Residue Values ("Outliers") in Crop Field Trial or Monitoring Data

As with the food consumption data, some have stated that the residue data included in Monte Carlo assessments have not been properly evaluated to identify potential errors in the data sets or to assess the potential impacts of these outliers on the estimate of the 99.9th percentile risk. OPP acknowledges that it is not uncommon, when field trial residues comprise the data sets used in a probabilistic assessment, that these data include one or more residue values which are significantly higher than the other measured concentrations. Just as with food consumption data, it is important to assure that these data are as accurate as possible. Retaining an erroneous high-end value may result in overestimating exposure, but discarding accurate high-end values may lead to an underestimate of exposure.

Frequently, high-end field trial values are the same data initially provided to the Agency by a pesticide company to support OPP's original decision to allow marketing for its product. In fact, these high end residue values likely were used in establishing EPA tolerances. Occasionally, these outliers have represented a sizable fraction of the submitted data sets.

Even though OPP may previously have reviewed and relied on a data set, because of the recognized potential impacts outliers could have on the high-end exposure estimates, each pesticide residue point in the residue data sets included as input to any Monte Carlo analysis is carefully reviewed and verified by OPP staff scientists. OPP's longstanding approach to outliers has been articulated in the recent draft document "Guidance for Submission of Probabilistic Exposure Assessments to the Office of Pesticide Programs." The decision to discard an outlier is based on a scientific or quality assurance basis, and is only made with extreme caution, particularly for environmental data sets which can often contain legitimate extreme values. OPP believes that statistical tests can be used to identify suspect data points which require further investigation, but that it is inappropriate to eliminate outliers from analysis on this basis alone unless further review of the suspect data points reveals a significant mistake in protocol which renders a generated residue value irrelevant to label conditions (e.g., wrong tank mix concentration, mistaken application rate, too early a PHI, too many applications, etc.) or there is some other basis to conclude that the data point is not appropriate for use. This is particularly true in cases where the data points in question have been used by the Agency in establishing a tolerance or other regulatory limit.

Occasionally, high-end values may be found among the data from the USDA or FDA monitoring programs. The Agency relies on the extensive QA/QC procedures followed by USDA's PDP program and the FDA program to determine which data points should be retained. Therefore, OPP normally does not discard any of these values, absent other evidence of their

invalidity. For example, the monitoring data provided by USDA's Pesticide Data Program are collected under rigorous QA/QC procedures which include method validation (determination of limit of detection and limit of quantitation for each pesticide/crop combination), confirmation of residue identity by alternate detection system, use of blanks, spikes, and internal and external standards, and verification of the analyst's performance (check samples, audits, etc.). Similarly, FDA uses official analytical methods that include blanks and fortifications, and requires confirmation of residues of regulatory significance by use of an alternate detection system and verification of results by a different analysis. These measures are intended to ensure integrity of monitoring data from the sample collection to data reporting.

As with consumption outliers from the USDA food consumption survey, OPP scientists will, as part of the risk characterization, inform the risk manager if such residue values are driving the upper ends of the exposure using DEEM's CEC analysis. If specific pesticide residues on certain crops substantially contribute to the majority of the exposures above the specified percentile, the risk manager can incorporate this information into the risk decision and determine an appropriate Agency response.

C. Representativeness

OPP combines both residue data (from crop field trials, monitoring programs, and market basket surveys) and food consumption data (from USDA CSFII surveys), using the DEEM computer software program to generate estimates of the distribution of daily exposures to pesticide residues in food for the general U. S. population and 26 specific subgroups within the U. S. population. The reliability of the estimate of the distribution of exposures depends on the quality of the data used in the model. The data sets used must be sufficiently representative to support reliable estimates.

The relationship between representativeness and the reliability of estimates of the distribution of exposure is easy to understand. Even if all of the values in a data base are accurate (see discussion in II A. and II B.), the use of a data set in a probabilistic assessment will produce unreliable exposure estimates to the extent that the data sample is unrepresentative of the larger population it purports to represent. For example, if no one from low income groups were interviewed about their eating habits, the survey results would miss the very real impact that income has on dietary choices.

The food consumption data used by OPP are collected by the USDA through a survey that is carefully designed to assure that the results would be representative of the U. S. population. The survey design specifically requires that samples be collected from people who differ in ways that could affect the types and amounts of foods they eat. For example, the survey covers people of different ages, genders, ethnicity, regions of the country, and socioeconomic status. People who are selected for interviews are contacted on different days of the week, scattered throughout the year to capture differences due to the time of year or day of the week. A number of other aspects of the survey are also controlled in order to maximize the prospect that

the results are representative not only of the entire U. S. population, but also particular subgroups, including those for which OPP generates acute dietary exposure distributions. (A full description of the survey methodology, including a discussion of the survey design characteristics that assure representativeness, is available from [cite].)

While the USDA food consumption surveys are designed to be generally representative of the U. S. population, it is clear that some factors that can influence dietary choices are not addressed in the survey design. For example, the CSFII surveys do not purport to be representative of people in institutional living arrangements (colleges, nursing homes, etc.) or of different religions or health status. In addition, concern has been expressed about how "representative" the survey results are at the high ends of consumption. This concern, in effect, involves the size of the food consumption data bases. The Agency addresses this concern in Section II.D. of this issue paper and proposes an approach to validate the use of the entire distribution in Section IV.

The various data bases on pesticide residues in food raise different set of issues with respect to "representativeness." If market basket or monitoring data are not available, OPP will use residue data sets generated by the registrants and submitted to the Agency for tolerance-setting purposes. The field trial studies are designed to follow the directions on the product labeling and are required to be performed in different areas of the country where the crop on which the pesticide is being used is grown. Multiple field trial sites are required if the crop is a significant component of the diet (e.g. wheat, corn, tomatoes, etc.) and if it is grown in geographically and climatically distinct regions. Of necessity, these are conducted at maximum label rates and minimum label pre-harvest intervals in order to establish maximum legal residue limits (tolerances) on food. Thus, the data set resulting from the required field trials represents the distribution of residues that are likely to be found in a particular raw agricultural commodity following a maximum label application scenario. But, due to the design of these field trial studies, the data are not likely to be representative of the residue values in food, as consumed. As discussed in section I.C.3., adjustments can be made to these data to better represent the amount of pesticides actually used (incorporating, for example, the range of typical application rates and typical PHI's and percent crop treated). Further adjustments and refinements can also be made to better reflect actual exposures: these can include cooking studies, residue degradation studies, washing/home processing studies, etc.

An even more representative picture of the amounts of pesticides in food to which the U.S. population is exposed can be obtained when OPP uses data from market basket surveys or from USDA PDP or FDA monitoring. These data sources are considered to be more "representative" of actual exposure to consumers than field trials conducted under conditions using maximum rate, minimum PHI, and other use conditions likely to lead to the highest lawful residue. Market basket surveys, for example, are statistically designed and are conducted on a single-serving basis at the point of sale to consumer. These types of studies, thus, best reflect those residues to which consumers are actually exposed. The USDA, too, exercises great care to assure that the food items sampled in its PDP program are representative of the large majority of

that type of agricultural commodity sampled in the country. These monitoring data are also designed to be statistically representative of commodities which are typically available throughout the year, except that they represent five pound composite samples (and not single-serving items) collected at distribution points just before release to supermarkets and grocery stores. In addition, PDP commodities are washed, peeled, de-stemmed, or cored, as appropriate prior to laboratory analysis to represent typical consumer practices. FDA surveillance monitoring data are geared more to tolerance enforcement and not toward OPP's risk assessment needs. Collection occurs as close to the farm gate as possible and the program is not designed to generate statistically representative samples for use in risk assessments. Due to sampling and collection methodologies, residues measured under the FDA surveillance monitoring program likely overestimate pesticide residues to which consumers are exposed. Nevertheless, they are considered more representative of residue levels to which consumers are exposed than the experimental field trial data submitted for tolerance-setting purposes.

D. Size of the Input Data Bases.

In addition to being accurate and representative, the data sets must also be sufficiently large to permit characterization of the overall exposure of the population of interest. The 1989-91 USDA food consumption survey includes data from 15,128 individuals. As noted earlier, each person was asked to contribute information for three different days. While not every respondent provided the full three days of responses, the CSFII data base collectively represents food records for a total of 35,712 unique person days. Moreover, since each person typically eats many different types of food during a day, there are a great many data points for consumption of specific foods in the data base. The following table summarizes the same information for several of the 27 populations that OPP evaluates in its probabilistic exposure assessments.

Size of 1989 - 91 CSFII Data Base		
Population Group	Number of Respondents (all three days)	Number of Respondent-days
U.S. Population	11,904	35,712
Infants <1	151	453
Children 1-5	1,060	3,180
Children 6-11	1,172	3,516
Females 12-49	4,019	12,057
Males 20+	3,381	10,143

Despite the overall large scope of the USDA CSFII database, some contend that USDA survey population sample sizes are insufficient size to provide reliable estimates at the high end of

exposure and risk, and that there is a need for specific OPP criteria for a minimum number of samples before an estimate is derived and used in establishing policy. The major focus of this discussion has been the small number of data points at the extremes of the consumption distribution for any given commodity. In other words, a very small number of people reported having eaten a food containing a particular commodity. Some state, in particular, that for many infrequently-consumed commodities or for small population subgroups, an adequate number of individuals is not available to calculate a high end consumption percentile. They say, therefore, that the percentile exposure represented by high end consumers of infrequently eaten foods is highly uncertain. They further note that USDA has identified minimum population sample size criteria for estimating various percentiles of food consumption, and recommended that USDA flag estimates that do not meet these criteria. They believe that OPP should not use data points that would fall at a percentile which would be flagged by the USDA. Rather, they argue that such high end (and "uncertain") values should be discarded (or otherwise adjusted) prior to using the data set to perform probabilistic exposure analyses.

OPP recognizes that there are limits with respect to the USDA food consumption data base which would affect the reliability of estimates of high-end consumption of particular commodities. In particular, for many infrequently-consumed commodities and for small population subgroups, an adequate number of individuals may not be available to calculate a reliable high-end consumption percentile[3]. OPP's interim position is to regulate at the 99.9th percentile of ***exposure***. This is not the 99.9th percentile of overall food ***consumption*** or of any one food item.[4] As discussed more fully below, the concern about the size of the input data base is not directed at whether the data sets are adequate to define high-end percentiles of pesticide residue levels in a *particular* food or consumption of a *specific* food form. Rather, the concern is whether the data bases are sufficiently large to characterize accurately the distribution of daily pesticide exposures from all foods which an individual eats in any given day. The distinction between estimating high-end percentiles of exposure and high-end percentiles of consumption (or residue) for a particular commodity is an important one. It may be that the part of the exposure

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[3] The Agency and USDA, together, recognize this as an issue and have initiated a Supplemental Children's Survey (SCS) for the 1994-1996 USDA CSFII. The 1994-96 CSFII contains data for approximately 5700 children up to 18 years of age and the CSFII-SCS will provide intakes on approximately 5000 additional children through 9 years of age, based on OPP sample size needs. The sample design is the same as that used for the 1994-96 CSFII so that the data from the SCS can be merged with data from the 1994-96 CSFII. In addition, we note that the next food consumption survey will be conducted jointly by USDA and CDC's National Center for Health Statistics (NCHS) and is expected a sample a greatly expanded number of persons.

[4] This difference is significant; the 99.9th percentile of exposure represents the joining of each individual's consumption data set with randomly selected residue data. Therefore, the individual at the high end of exposure could be associated with mid- or low-end consumption and mid- or high-end residues, or vice versa. The high end of estimated exposure thus represents the combination of the two data sets.

distribution which is derived from (or includes) any single (presumably uncertain) upper-end USDA *consumption* value, does not necessarily produce an invalid *exposure* value. Many of the upper-end exposure estimates might not contain upper-end USDA consumption values and thus these uncertain USDA *consumption* values may not be driving the high-end Agency *exposure* estimates at all.

Although this concern might need to be heightened when OPP's probabilistic exposure assessments involve only a single commodity with few residue data points, one or even a few very high food consumption values do not appear likely to be the primary driver(s) of exposure and disproportionately influence the outcome of the DEEM exposure estimates (see Section IV of this document - "Next Steps by EPA and USDA" - for a proposed testing protocol). The more commodities which are included in the analysis, the more unlikely it is that the upper-end exposure values are driven by upper-end USDA consumption values.

Finally, as discussed above with respect to the accuracy and representativeness of the input data bases, OPP will perform a sensitivity analysis on all probabilistic assessments of dietary exposure. The CEC module will identify the critical input data points, and the Agency can decide whether to rely on the estimates of high-end exposure in its risk management decisions.

E. Impact of Agency Default Assumptions on the Choice of a Percentile Exposure Estimate for the Threshold of Concern

Some contend that the use of conservative default assumptions by OPP in its treatment of pesticide residue data results in the estimate of the 99.9th percentile exposure being significantly higher than the actual 99.9th percentile exposure. They point specifically to OPP's use of maximum rate/minimum pre-harvest interval field trial data in the exposure assessment, OPP's treatment of non-detects, and its use of 95th percentile data from monitoring studies . OPP agrees that these three assumptions would lead to an overestimate of dietary exposure, but OPP uses these assumptions only in its lower tiered, screening assessments. OPP's policy is to rely on a screening estimate of exposure only if the estimate indicates that risk would be acceptable. Because such screening estimates overstate exposure, OPP refines its exposure and risk assessments using more realistic data. These refined, higher tiered estimates do not use the conservative default assumptions likely to overestimate risk. For more information on these tiers, see "Guidance for the Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs " (63 FR 59780).

With respect to the Office's use of field trial data, OPP prefers (when appropriate and available) to use data from market basket surveys, or PDP or FDA surveillance monitoring data in conducting its pesticide exposure assessments rather than from field trials. However, these market basket or monitoring data are not always available or appropriate for use. When exposure data are obtained from field trials, these data can be modified or adjusted to take into account decreasing or increasing concentrations in processed commodities as a result of commercial processing practices or decreased residues as a result of cooking or in-home

preparation such as washing, peeling, coring, etc. OPP is also able to incorporate information about lower than label-specified application rates and longer than label-specified pre-harvest intervals, if available.

Concerning the Office's treatment of non-detects, OPP has issued two draft papers regarding proposals for handling these type of data: "Assigning Values to Nondetected/ Nonquantified Pesticide Residues in Human Health Dietary Exposure Assessments," 63 FR 67063; and "A Statistical Method for Incorporating Nondetected Pesticide Residues into Human Health Dietary Exposure Assessments" (63 FR 67063). In the first paper, the Agency is proposing to use ½ the limit of detection (LOD) (in place of the full LOD or the limit of quantitation (LOQ)) for treated commodities in cases where the limit of detection has been adequately documented. As explained in the science policy paper, empirical data indicate that it is very realistic to assume that treated non-detects contain residues equal to ½ LOD. The Agency will also be performing sensitivity analyses which can determine whether the assumed residue value assigned to the non-detect values is driving the risk estimate. In the second paper, OPP has presented a proposal for dealing with residue data sets in which many of the observations are below detectable levels. OPP believes that these refinements in the treatment of non-detects will alleviate many of the perceived overly-conservative biases in exposure estimates with regard to the assigning of values to non-detects.

With respect to concern about use of the 95th percentile residue value from monitoring data, this policy has recently been revised. Prior to the availability of the probabilistic software, a registrant could, for blended commodities such as corn, soybean, wheat, etc., use either average crop field trial concentrations (which reflect the maximum label use scenario) adjusted for percent crop treated **or** 95th percentile FDA or USDA monitoring data in its acute risk assessment. Either of these would be entered as a *point estimate* for use in an acute risk assessment. The 95th percentile monitoring data had been introduced as an alternative to the use of average field trial concentrations since it was believed that this would be a more realistic (but still conservative) estimate of actual exposures which would take into account actual use practices. With probabilistic software now available the Agency is no longer required to rely solely on point estimates of residue values in its acute dietary risk assessments, and this policy has been revised accordingly. The Agency no longer uses a 95th percentile point estimate from monitoring data for blended commodities but instead, uses *the entire range* of monitoring data and therefore incorporates *the entire distribution* in its exposure assessment using all of the available monitoring data. Thus, the concern about OPP reliance on upper end (95th percentile) monitoring data for blended commodities in its risk assessments is no longer justified -- OPP uses the full set of monitoring data thereby fully incorporating the most refined concentration data available.

III. Issues Related to Public Health Policy

The FQPA directs EPA to set or retain tolerances for a pesticide only if the Agency determines that there is "a reasonable certainty of no harm" from dietary and other non-occupational sources of exposure. OPP will use available and reliable scientific information to

characterize the toxicity and exposures of a food use pesticide in deciding whether a particular pesticide meets the FQPA safety standard. Put simply, OPP's goal is to regulate pesticides in such a manner that everyone is reasonably certain to experience no harm as a result of dietary and other non-occupational exposures to pesticides.

To implement this statutory standard, OPP has to make a risk management judgment about what level of pesticide residue in food is consistent with this standard. OPP has decided to express its risk management judgment for acute dietary risks in quantitative scientific form, as a "threshold of concern." A threshold of concern for acute dietary risks, when based on probabilistic exposure estimates, has two elements: (1) a percentile (or proportion) of the population for which exposure to a specific level of pesticide residue must be "safe;" and (2) a benchmark for judging a safe level of exposure. OPP's interim policy is to set its threshold of concern for acute dietary risk to pesticides such that the 99.9th percentile of estimated daily exposure, using probabilistic exposure estimation techniques, must be equal to or less than the Population Adjusted Dose (PAD). The PAD will be used as the benchmark of safety. The rest of this section discusses OPP's rationale for choosing the 99.9th percentile and the concerns that have been expressed about that choice.

In adopting this interim policy, the Office recognizes that the choice of the threshold of concern requires a balancing of a number of factors. OPP must consider the size of the exposed population and the proportion which might receive daily doses above the benchmark of safety, the PAD. The Agency must also weigh the level of confidence it has in its exposure estimates, and the extent to which such estimates may overstate (or understate) potential exposure because they incorporate conservative assumptions or rely on atypical and unrealistic data. Further, to the extent understood, OPP needs to consider by how much individual exposures would be estimated to exceed the PAD. Finally, the Agency must take into account the degree of public health protection incorporated into the determination of the aRfD and the PAD.

In initially determining where to establish the ***threshold of concern***, OPP considered a number of issues and past practices, including the 1992 Guidelines for Exposure Assessment (57 FR 22888-22938). These Guidelines established a broad framework for Agency exposure assessments by describing the general concepts of exposure assessment and by providing guidance on the planning and conduct of an exposure assessment, including the characterization of uncertainty. Specifically regarding the use of high percentile values, the Agency in these exposure assessment guidelines has stated the following:

> Although the Agency has not specifically set policy on this matter, exposure assessors should observe the following caution when using simulated distributions. The actual percentile cutoff above which a simulation should be considered a ***bounding estimate*** may be expected to vary depending upon the size of the population. Since bounding estimates are established to develop statements that exposures, doses, and risks are "not greater than...", it is prudent that the percentile cutoff bound expected exposures for the population being evaluated. For example, if there are 100 persons in the population, it may be prudent to consider simulated exposures above the 1 in 500

level or 1 in 1000 level (i.e., above the 99.5th or 99.9th percentile, respectively) to be bounding estimates. Due to uncertainties in simulated distributions, assessors should be cautious about using estimates above the 99.9th percentile for estimates of ***high-end*** exposures, regardless of the size of the population. The Agency or individual program offices may issue more direct policy for setting the exact cutoff value for use as high end and bounding estimates in simulations.

Taking the Agency guidance into account, and giving significant weight to the size of the exposed population, OPP uses as a threshold of concern the following level for purposes of its interim approach: the 99.9th percentile of estimated daily exposure, using probabilistic exposure estimation techniques, should be equal to or less than the Population Adjusted Dose (PAD). Under this interim policy, when the 99.9th percentile of estimated exposure is equal to or less than the PAD, the vast majority of people would not be exposed to pesticides in their food at unsafe levels. Only those individuals whose exposure is estimated to be in the high end of the exposure distribution might receive amounts of pesticide in their food that even approached the level where concern would exist. Based on OPP's experience reviewing Monte Carlo acute dietary exposure estimates, it appears that those with significantly lower exposures (i.e., at lower percentiles of estimated exposure) would be consuming levels of pesticide in their food potentially several orders of magnitude below the PAD. In other words, for example, if exposure estimated at the 99.9th percentile equaled the PAD, estimates of exposure at the 90^{th} percentile might be from 10 to perhaps as much as 50 or more times lower.

Some people, however, have argued that OPP's interim policy is not sufficiently protective, even at the 99.9th percentile of exposure. Because the group eating food containing pesticide residues is very close, if not equal, to the entire population of the country, currently about 272 million people, they argue that if the 99.9th percentile of exposure is equal to the PAD, very large numbers of people, including many children, could be exposed at levels which exceed the PAD each day. Thus, they argue for additional protections to be provided in the risk assessment or risk management process.

While OPP recognizes that, under this policy, a large number of people – particularly infants and children – would theoretically be exposed at levels potentially exceeding the PAD, the Agency believes, for several reasons, that allowing this level of estimated exposure would not raise public health concerns. First, the Agency believes that actual exposure is unlikely to be greater than that estimated, and in most cases would actually be somewhat lower than the estimates based on data currently available. As discussed in this and other papers, OPP uses a tiered approach and the best available data to develop estimates of exposure to pesticide residues in food. Monte Carlo techniques are used in the EPA's highest, most refined tiers – the tiers which are designed to provide the most realistic estimates of exposure. Nonetheless, at the present time, because of data limitations, even the most refined estimates of exposure may still include residue values for one or more commodities that are higher than people actually consume. For some pesticides, for example, the Agency may not have residue monitoring data, such as USDA's PDP data. In such cases therefore, the exposure estimated at the 99.9th percentile (or

any other percentile) may overstate potential exposure, and some portion of the most highly exposed 0.1% of the population would actually be getting exposure less than the PAD. (While this conservative quality in a higher tier exposure estimate is unavoidable except through creation of better data, OPP does not believe that it significantly overstates exposure. The sensitivity analysis of Critical Exposure Contributions will identify the extent to which high residue values for specific commodities account for the upper end of exposure.)

Second, exposure at a level above the PAD would pose public health concerns only to the extent that such exposures might result in harm. Certainly it would be difficult to justify allowing a very large number of individuals to get doses of a pesticide at such levels, if OPP expected all such exposures to result in harm. However, OPP believes that its risk estimation methods incorporate sufficiently conservative (health protective) approaches, so that the overall approach provides sufficient protection for the small percentage of people (those above the 99.9th percentile) who may be exposed above the PAD. OPP sets the aRfD well below (usually 100 to 1000 times lower than) the appropriately-chosen "no observed adverse effect level" (NOAEL) in the most relevant laboratory animal toxicity study: the PAD may be the same as the aRfD or even lower depending upon the FQPA 10x Safety Factor decision. Thus, an exceedence of the threshold of concern does **NOT** automatically mean that people are being exposed to unsafe levels of pesticide residues in food or that an individual will necessarily experience any adverse effects.

Third, from information about the general shape of the distribution curve of dietary exposures, OPP expects the vast majority of individuals estimated to be exposed to residues over the aRfD or PAD would be exposed only to levels slightly greater than the aRfD or PAD. Thus, for the majority of the exposed individuals who are exposed to levels over the aRfD or PAD, their exposure would still be well below the relevant NOAEL.

Fourth, given the size of the exposed population, the occurrence of an "exceedance" would (at the 99.9th percentile level) be very infrequent for the typical individual. For example, at the 99.9th percentile, time between exceedances, on average, would be once every 2 to 3 years. Depending on an individual's diet, an exceedence may occur more or less frequently. Collectively, this information gives the Agency confidence that its approach to protecting people from risks associated with single-day exposure to pesticides in their diet is adequately protective.

Some have asserted that OPP's interim policy is overly protective. One concern is that the Office's exposure methodology significantly overestimates actual exposure to the extent that the underlying data bases include outliers or unrepresentative (and unrealistically high) field trial residue data. A closely allied concern is that exposure estimates overstate exposure when the methodology uses unrealistic, conservative assumptions. These concerns are addressed in section II of this paper, and as discussed there, efforts are made to use only reliable, realistic data. Because of the careful quality control measures taken by USDA and FDA in the generation of food consumption and residue monitoring data, OPP typically accepts those data sets compiled by the respective agencies as being reliable and realistic. OPP conducts its own review of residue

data from field trials and adjusts these data to better reflect actual residues on food. As discussed in section II.E., OPP believes that it does not use overly conservative assumptions. In sum, the Office does not believe that the data bases used, and the ways in which they are used to develop probabilistic exposure estimates, will produce significant overestimates of exposure at the 99.9th percentile.

A second concern is that the data bases available for use in probabilistic exposure estimates yield estimates at the 99.9th percentile that are unacceptably uncertain, and because of the uncertainty, OPP should use a lower percentile (e.g. the 99.5th, 99th, or 95th percentile) of exposure in its expression of the threshold of concern. While OPP agrees that the estimates of the 99.9th percentile of exposure have some uncertainty due to the use of high-end consumption and/or residue data, the Office does not know whether the probabilistic assessments understate or overstate actual exposure at the 99.9th percentile. Nor is the Office certain that one high-end residue or consumption value will "drive" high-end exposure estimates. In order to evaluate the possible impact of high-end values, OPP will perform sensitivity analyses at the threshold of concern to determine what data account for the largest part of the estimated exposure. In any event, because of the uncertainty of high-end estimates, OPP has considered whether to set its threshold of concern at a lower percentile of estimated exposure.

If OPP adopted a policy that relied on a percentile of exposure lower than the 99.9th percentile, it would need to justify its decision in public health terms as being consistent with the FQPA statutory standard. As indicated above in the discussion of whether the 99.9th percentile of exposure is adequately protective, the choice of any percentile less than 100% assumes that, to the extent that estimates understate or correspond to actual, real world exposure, some portion of the exposed population could receive an amount of pesticide in excess of the PAD. As lower percentiles are considered, the size of the population potentially exposed to levels greater than the PAD increases. Furthermore, if a lower percentile of regulatory concern were selected, a greater proportion of the population would be exposed more frequently to a one-day pesticides intake which exceeds PAD by a greater margin. For example, at the 99th percentile of exposure, on average, individuals would experience an exceedance roughly once over several months. Moreover, the size of the exposed population potentially exceeding the PAD at the 99^{th} or 95^{th} percentiles would be 10 and 50 times larger, respectively, than the number at the 99.9th percentile.

In the Office's view, the above analysis raises concerns about using a lower percentile than the 99.9th. If, because of uncertainties associated with using the 99.9th percentile, the Office decided to use a lower percentile of exposure as its threshold of concern, OPP would still have some uncertainty in its assessment of acute dietary risk. At the lower percentiles, the predicted incidence of these exceedences is quite high, and there is a substantial possibility that some significant number of people would be receiving doses that are considerably higher than the PAD. But OPP would not have much certainty about either the number of people above the PAD or, more importantly, how close to the aRfD or NOAEL their exposures come. Therefore, if the Office chose a lower percentile as its threshold of concern, OPP would also need to consider

whether other steps (e.g. use of an additional safety/uncertainty factor) would be needed to assure that the FQPA safety standard was satisfied.

IV. Next Steps by EPA and USDA

While OPP continues to apply its interim policy to regulatory decisions, OPP recognizes that there is considerable concern about both the scientific and regulatory judgments underpinning the policy. Many of the scientific concerns result from questions about how this relatively new approach to assessing acute dietary exposure will be performed and what aspects of the methodology have the greatest impact on the outcome. In fact, reliance on probabilistic exposure modeling techniques in regulatory decision making has very few precedents.

Therefore, OPP has decided that further analysis of the methodology would provide both the Agency's staff and the public with a better understanding of the most critical elements of the methodology. OPP, in consultation with USDA, is planning several analyses to evaluate a variety of statistical attributes of the distributions produced using the Monte Carlo technique. Specifically, OPP will use data sets on several currently registered pesticide to evaluate: (1) the impact of the number of commodities on the assessment; (2) the significance of the atypical food consumer on the estimates of high-end exposure; and (3) the variability of the output distribution at various percentiles at the high end of the distribution. To address these questions, the following steps will be taken:

Step 1: Conduct a series of exposure assessments to examine the individuals with estimated high-end exposures for a given chemical, beginning with one commodity and increasing stepwise to several commodities to see whether and how the identity of consumers at the high-end changes. In this step, OPP will attempt to identify individual consumers who occur to a disproportionate extent at the high end. The Agency will then examine the consumption diaries of these high-end consumers to see what aspect of their reported consumption is driving their appearance at the high end of the distribution.

Step 2: Having identified a high-end consumer who exhibits some atypical pattern of consumption, the Agency will remove data relating to this individual and will evaluate how the output distribution changes. This calculation will provide insight into the extent to which single, atypical consumption values impact the overall distribution of dietary exposures.

Step 3: A dietary exposure assessment will be conducted repeatedly to obtain a set of output distributions. Having obtained a set of outputs from identical input data sets, standard deviations will be calculated for selected exposure percentiles from the 95th to 99.9th. By doing this, the Agency will address the issue of variability of the output distribution at the high ends of the

exposure distribution.

Information collected from this process, and any information obtained during the public comment period, will be used to revise the policy document, as appropriate.

V. Request for Comments

1. What are the appropriate statistical techniques for characterizing the uncertainty at the high end of the distribution of probabilistic exposure assessments? At what point does an exposure estimate become so uncertain that it would be inappropriate to use the estimate in regulatory decision making? How does uncertainty about one or more high-end values in a data set affect the reliability of the output of probabilistic models using that data set as an input?

2. Regarding the Agency's current methodology for performing Monte Carlo analyses, at what percentile of estimated exposure is it appropriate for the Agency to establish its threshold of concern? 99.99th, 99.9th, 99th, 95th, or some other percentile? What are the reasons for recommending that percentile? How should the characteristics of the data sets used as input to the assessment (e.g., the type of residue data, field trials vs. PDP monitoring data) affect the choice of a percentile exposure for OPP's threshold of concern?

3. If OPP chooses to set its threshold of concern lower than the 99.9th percentile, should any other steps, such as the application of an additional safety factor, be employed to assure that the statutory safety standard is satisfied?

4. Some advocate a "sliding regulatory scale" with more serious toxic effects regulated at higher thresholds; they contend that such an approach would explicitly acknowledge all aspects of the risk management decision and incorporate the nature of the toxic effects and the built-in conservatism on the hazard identification and dose response side of the equation. Instead of regulating at only a single percentile for all toxicological effects (regardless of severity), should the Agency regulate pesticides at a variety of percentiles, depending upon the toxic effect observed? For example, would a lower threshold of regulation (perhaps the 98th percentile) be warranted for fully-reversible effects (such as mild anemia) or would a more stringent threshold (perhaps the 99.9th percentile or higher) be justified for severe, non-reversible effects (e.g., birth defects)? Finally, should the Agency regulate pesticides at different percentiles according to the nature and size of the subpopulation groups (i.e., use the 99.9th percentile for larger groups and another percentile for smaller groups)?

5. How should "outliers" be identified for food consumption data sets? For residue data sets? When an "outlier" is identified, how should the data point be handled in generating probabilistic exposure estimates?

6. If OPP conducts a Critical Exposure Contribution analysis, and excludes one or more data points because they appear to drive the high-end estimates of exposure, should OPP perform an

additional CEC analysis on any revised estimate of the exposure distribution?

7. Should OPP's probabilistic assessments attempt to reflect variability in human sensitivity to toxic effects, as suggested by the FIFRA SAP? If so, how should this be done?

VI. Bibliography

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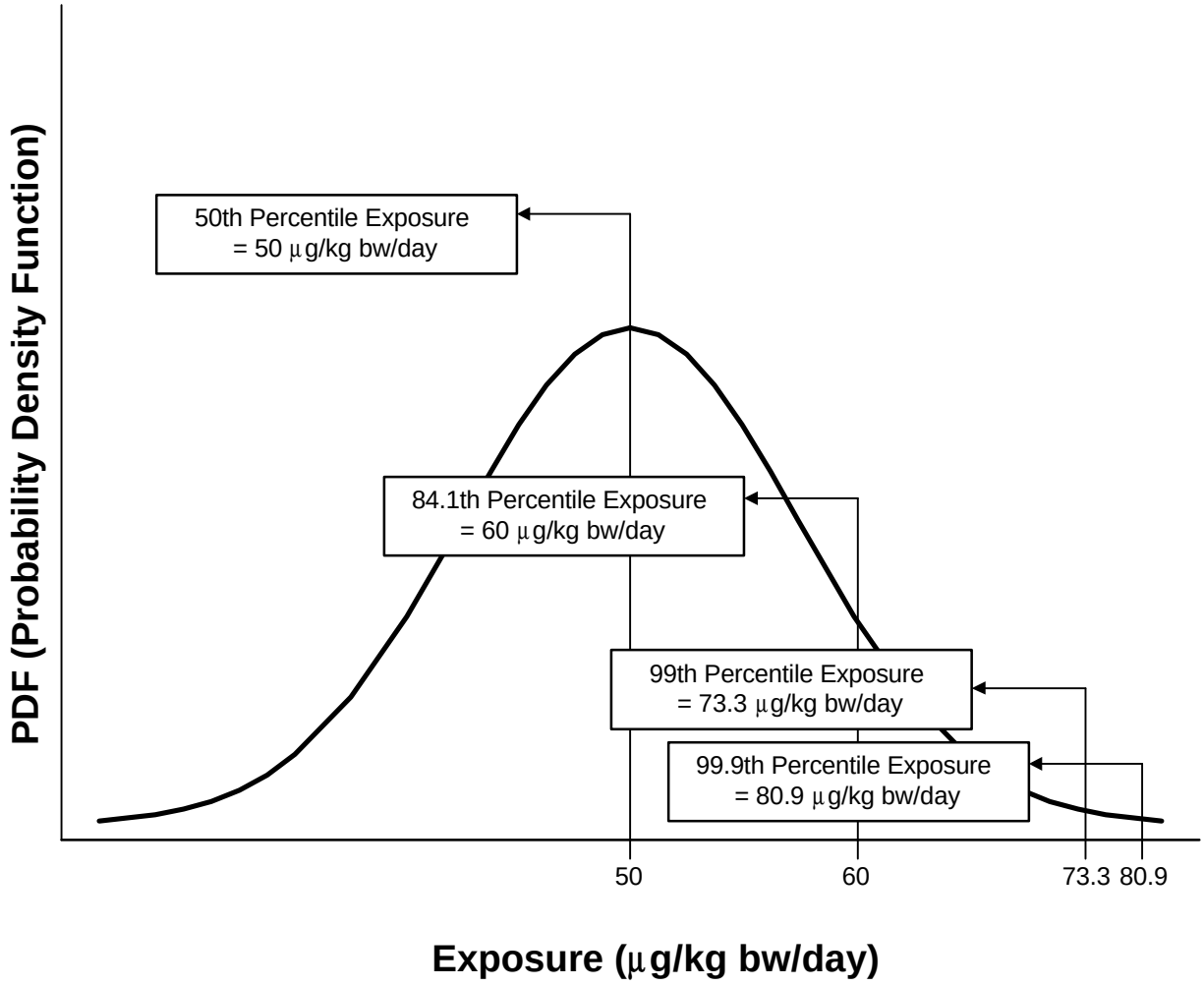
APPENDIX

Primer on Interpretation of Exposure Distribution Curves

Traditionally, OPP has selected a threshold of regulation (e.g., an individual cancer risk of no greater than 1-in-a-million or a %aRfD of no more than 100%) which could not be exceeded, and calculated a high-end (or bounding) point estimate of exposure using certain high-end exposure assumptions. This high-end exposure estimate was then combined with the toxicological endpoint to determine whether a hypothetical "high-end" individual exceeded the regulatory threshold of concern. If so, exposures were deemed to be unacceptable and mitigation actions were required. However, it was not known where in the exposure distribution OPP's "high-end" exposure estimate was located. That is, it was not known whether this estimated exposure represented the 95th, 99th, 99.9th, or 99.999th percentile individual or if the high-end exposure estimates were well beyond the exposures received by even the maximally exposed individual (i.e., if high-end exposure estimates were above the 100th percentile).

With the advent of Monte Carlo analysis, the OPP is no longer limited to assessing dietary exposure

and risks to the population using methodologies which produce only a single high-end point estimate. Monte Carlo analyses permit the risk assessor to not only produce more accurate estimates of ,but to produce estimates of exposure across the entire population which incorporate the *probabilities* of being subjected to these exposures. This distribution of exposures can be represented graphically as a probability density function similar to the classic bell curve. An example of one of these curves is illustrated on the following page:


PDF (Probability Density Function)
50th Percentile Exposure
= 50 µg/kg bw/day
84.1th Percentile Exposure
= 60 µg/kg bw/day
99th Percentile Exposure
= 73.3 µg/kg bw/day
99.9th Percentile Exposure
= 80.9 µg/kg bw/day
50
60
73.3
80.9
Exposure (µg/kg bw/day)

The total area under the curve represents the entire population of interest. As one moves progressively from the extreme left side of the distribution (from an exposure of zero) to the right, an ever higher proportion of the population falls under the curve. As can be seen, 50% of the population is exposed to levels of 50 μg/kg bw/day or less, 84.1% of the population is exposed to levels of 60 μg/kg/day or less, 99% of the population is exposed to levels of 73.3 μg/kg bw/day or less, and 99.9% of the population is exposed to levels of 80.9 μg/kg bw/day or less.

In the above bell curve example, the exposures across the population range from a low of about 10 μg/kg bw/day to a high of about 90 μg/kg bw/day, with a mean (or average) exposure of 50 μg/kg bw/day. Also, exposures at the 50th, 84.1th, 99th, and 99.9th percentiles are 50-, 60-, 73.3-, and 80.9- μg/kg bw/day, respectively. Each of these exposure values (in μg/kg bw/day) can be converted to a %PAD (to be compared to the threshold of concern) which is calculated by dividing each exposure value by PAD. These %PADs are calculated and shown in the table below:

Hypothetical Calculation of %PAD at Various Percentile Thresholds of Concern

Percentile Threshold of Concern	Estimated Exposure at Specified Percentile Threshold of Concern[a] (μg/kg bw/day)	PAD[b] (μg/kg bw/day)	%PAD[c]
99.9	80.9	75	108%
99	73.3		98%
84.1	60		80%
50	50		67%

[a] Obtained as output from DEEM software program

[b] This is calculated by dividing the NOAEL observed in animal studies (in μg/kg bw/day) by the appropriate uncertainty factors, and a decision with regard to the FPQA 10x Safety Factor. In this hypothetical case, the NOAEL is 7500 μg/kg bw/day , the uncertainty factor is 100, and the FQPA Safety Factor has been removed..

[c]The %PAD is calculated by dividing the estimated exposure at any given percentile by the PAD. In general, a %PAD of 100% or less is not considered to be of concern, if the FQPA 10x Safety Factor has been removed and animal data provide the basis for the aRfD.

From the above table it is apparent that the %PAD corresponding to the 99.9th percentile of exposure (at 108%) exceeds the threshold of concern. It is also apparent that "acceptable" exposures would occur at the 99th percentile. Thus, exposures would be deemed excessive if the 99.9th percentile is considered to be the threshold of concern and either mitigation of exposures (or refinement of exposure estimates) would be required.